Protein Conformation I

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Molecular Dynamics Study of Phosphorylation Mediated Structural Changes in Neurofilament Medium (NF-M) Subunit

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Neurofilaments (NFs) are essential building blocks of axonal architecture. Abnormal behavior of these cytostructural elements has been associated with several neuromuscular disorders such as Amyotropic Lateral Sclerosis (ALS). NFs are assembled from three subunits: Low (NFL), Medium (NFM) and Heavy (NFH). These subunits are characterized by a common alpha helical rod domain and carboxyl terminal domains of different lengths specific to each subunit. The tails project from the core of the filament and contain a number of KSP repeat motifs that belongs to the sites for phosphorylation. Especially, the C-terminal tails of NFM and NFH that have relatively longer lengths and higher number of KSP repeats were found to be the key participants of the sidearm-mediated interfilament interactions that regulate the axonal diameter. Though it has been established that that the sidearms play a key functional role, little is known about the roles of individual subunits and the effect of phosphorylation on their behavior. Initially, it was believed that the NFH sidearms play a more integral role in determining axonal structure due to the presence of longer polypeptides and relatively higher KSP repeat units. However, recent studies showed that deleting NFH from neurofilaments does not affect axonal diameter, suggesting that NFM may in fact be the key player. In view of this, it is essential to have an understanding of the morphological behavior of the NFM sidearm in response to physiological conditions. In the present study we carried out MD simulations of human and mouse NFM C terminals under different phosphorylation and ionic conditions. The results from these studies provide useful molecular level insight into the structural changes of NFM sidearms in response to phosphorylation, ionic concentrations. The present study reveals sidearm-mediated regulation mechanism of axonal caliber.

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Structural Determinants of Conformational Flexibility and Long-Range Allostery of the CRM1 Export Complex

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In eukaryotes the nucleocytoplasmic transport of macromolecules is mainly mediated by soluble nuclear transport receptors of the karyopherin-β superfamily termed importins and exportins. The prototypical and highly versatile exportin CRM1 (chromosome region maintenance 1) is essential for nuclear depletion of numerous structurally and functionally unrelated protein and RNP cargoes. CRM1 has been shown to bind RanGTP (GTP bound RAs-related nuclear protein) and cargo proteins in an allosteric manner and to adopt a toroidal structure in several functional transport complexes. It was thought to maintain this conformation, with N- and C-terminal regions in close proximity, throughout the entire nucleocytoplasmic transport cycle.
A recently solved structure of cargo-free CRM1 however revealed a superhelical, open conformation. Using molecular dynamics simulations, two distinct features of this conformation and their influence on the structural stability were investigated. One of those, the C-terminal helix, was identified as a major stabilising factor of the superhelical conformation.
We furthermore showed that the overall configuration of CRM1 influences the local configuration of the cargo binding site. Based on these results we suggest a mechanism for the observed cooperative binding.

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Characterizing the Molecular Mechanism of the Histidine Switch Model in Influenza Virus Hemagglutinin

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Hemagglutinin is a specific homotrimer glycoprotein on the surface of influenza virus envelope that consists of two subunits, HA1 and HA2. pH-mediated conformational changes of the HA2 chain play a key role in membrane fusion of the viral envelope to the host cell endosomal membrane. Two major steps are involved: first, formation a needle-shaped structure that inserts into the endosomal membrane from the N-terminus; second, re-bending of HA2 at a hinge region (residues 106 to 111) into a hairpin-shaped structure that brings the viral envelope very close to the endosomal membrane, thereby fusion of the two membranes. Following the histidine switch hypothesis, in order to characterize the molecular events taking place in the hinge region of HA2 in response to pH changes, we have performed molecular dynamics (MD) simulation of several hemagglutinin subtypes at neutral and low pH conditions, modeled by changing the protonation state of a histidine side chain located in this region. More than sixty sets of MD simulations (collectively amounting to 20 μs) of a 26-residue representation of the hinge-region were performed in implicit and explicit solvents to study the effects of histidine protonation. Bending of the hinge was observed upon protonation of the histidine in all models with an initial straight conformation, whereas the models with neutral histidine retained their primarily straight conformation. The MD simulations starting from an initially bent conformation resulted in the formation of a straight helical structure upon neutralization of the histidine, while the bent structure was maintained in the presence of a protonated histidine. Finally, mutation of the key histidine to alanine completely abolishes the bending of the peptide altogether.
Our results showed that histidine protonation is critical for low-pH conformational changes of the hinge region in HA2.

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Recognition of Chemotherapeutically Damaged DNA by Mismatch Repair Proteins

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Complementing scarce experimental data, we provide computational evidence via all-atom molecular dynamics simulations for conformational changes and dynamical changes induced in the MSH2/6 heterodimer in response to DNA damage induced by platinum-based chemotherapuetics. We demonstrate thay 1,2 and 1,3 intra-strand platinum-DNA adducts are recognized by MutSα in a similar manner, but with subtle differences which may play a role in the way the different damages are signaled by MutSα.

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Benchmarking the Water-Peptide Interaction

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The interaction between water molecules and the hydration sites of peptides is critical for any quantitative modeling of solvated peptides. We address this interaction for the successive hydration of two peptides for which accurate experimental reference data exist:Ac-Ala_5-$LysH^+$ (non-helical) and Ac-Ala_8-$LysH^+$ (helical). In particular, finite-temperature Gibbs reference water binding energies ΔG^0 and equilibrium constants are known [1,2]. In contrast, earlier force-field predicted preferred water binding sites do not agree with one another. We present an exhaustive first-principles study (density-functional theory based on the van der Waals corrected PBE functional) that demonstrates: (i) There is a close competition between possible hydration sites (protonated carboxyl group or ammonium group). The preferred first hydration site breaks an intramolecular bond of the ammonium group in the unsolvated molecule. (ii) Calculated $\Delta G^0(T)$ are in remarkable agreement with experimental data. Lowest-energy H_2O H-bond networks are predicted for up to five H_2O molecules, and the connection to the solvated state is explored by ab initio molecular dynamics with up to 152 H_2O molecules.
[1] Int. J. Mass Spec. 236, 81 (2004)
[2] J. Am. Chem. Soc. 126, 8454 (2004).

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Predictive Power of Conformational Motion

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Biological macromolecules are flexible and dynamic systems, continuously changing shapes in response to environmental or other factors. Each possible shape is called a conformation, and a transition between them is referred as a conformational motion. The conformational motion may be induced by many factors which in a sense of theoretical physics should be explained by equation of conformational motion. In previous presentation (Svintradze D.V. (2009) Conformational Motion of Biological Macromolecules. Biophys. J. 96, 584) we pinpointed the possibility of formulation the equation of conformational motion which would go beyond of biophysics and touch fundamental problems of physics. In upcoming presentation we would like to apply the equation to proteins and DNA and deduce fluctuation frequency of the macromolecules. Fundamental Theory has to be uniformly true for all dimensions and should extend current knowledge of physics so that equivalence principal has to hold good. The theory of conformational motion has such potential. In order to rigorously clarify the point we will derive Einstein field equation from equation